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Optimising outcomes in clozapine rechallenge following neutropenia: a cohort analysis.

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Abbreviations: ANC: absolute neutrophil count; WCC: white cell (leucocyte) count; BEN: benign ethnic neutropenia; G-CSF: granulocyte-colony stimulating factor; NPU: National Psychosis Unit

Keywords: clozapine, rechallenge, neutropenia, agranulocytosis, benign ethnic neutropenia, G-CSF

Abstract

Objective:
Certain patients with treatment-refractory schizophrenia may be rechallenged with clozapine following previous neutropenia. Evidence guiding patient selection and the effectiveness of lithium and granulocyte-colony stimulating factor (G-CSF) in rechallenge is limited, and factors associated with successful outcomes are unclear.

Method:
Outcomes were studied in patients rechallenged with clozapine at a tertiary referral centre between January 2007 – December 2013, following one or more previous trials terminated due to neutropenia, defined as an absolute neutrophil count (ANC) $<1.5 \times 10^9$/L. Demographic characteristics, details of each clozapine trial including ANC and co-prescribed medication were extracted and factors associated with rechallenge outcomes examined.

Results:
Nineteen patients underwent clozapine rechallenge following previous neutropenia; four (21%) experienced further neutropenia, two of which were agranulocytosis. Compared to successfully rechallenged patients, unsuccessful rechallenges were significantly older ($t=2.10$, $p=0.05$), onset of neutropenia was sooner ($W=10.0$, $p=0.03$), and valproate co-prescription was more common. In addition to five patients with benign ethnic neutropenia (BEN), 8/10 patients not of an ethnicity associated with BEN also had idiopathic low neutrophil counts at baseline; lithium and G-CSF co-prescription facilitated successful rechallenge in these patients.

Conclusion:
In this selected population, the initial neutropenia was unlikely to be related to clozapine in a substantial proportion of cases. This group was successfully rechallenged following careful consideration of the risks and benefits, and lithium and G-CSF contributed to allowing continued clozapine therapy. In addition to Black patients, other ethnic groups can have persistently low ANC unrelated to clozapine.

Introduction

Clozapine is an antipsychotic with unique efficacy in treatment-refractory schizophrenia[1]. In the UK, clozapine is recommended in patients who have failed to respond to trials of at least two different antipsychotics at adequate doses[2]. However, first-line use is limited by its propensity to cause neutropenia[3] and potentially fatal agranulocytosis[4] in 3% and 0.8% of patients respectively, and regular haematological monitoring is mandatory for all patients receiving clozapine. Patients developing haematological dyscrasia are excluded from further licensed treatment.

Nonetheless, in certain individuals where illness is severe and a good response to clozapine was observed, off-label rechallenge of clozapine may be attempted after careful consideration of the risks and benefits[5]. In particular, cases where the original dyscrasia was likely to have been due to factors other than clozapine may benefit from rechallenge. Co-administration of other drugs which interact with clozapine, or in themselves cause haematological toxicity, may account for, or contribute to, some cases of neutropenia[6]. Benign ethnic neutropenia (BEN) affects 25-50% of people of African ancestry, as well those of Arabic-Middle Eastern descent[7; 8], and has been recognised as a factor contributing to clozapine discontinuation in these populations[9]. The use of modified monitoring criteria for BEN populations[10], co-administration of lithium[11] and G-CSF[12] have been used to augment leucocyte counts and avoid treatment interruption or discontinuation.

Due to the risk of agranulocytosis, patients and clinicians are understandably hesitant to undertake clozapine rechallenge, and it remains uncommon. The evidence base guiding practice is correspondingly sparse. The largest study consisted of 53 patients rechallenged in the UK over a five year period[13], of whom 20 (38%) experienced a further dyscrasia, nine of which were agranulocytoses. No clear risk factors for repeat dyscrasia were identified, however the second dyscrasia was more severe, more prolonged and occurred sooner. Kanaan and Kerwin[14] studied 25 rechallenges with co-prescribed lithium, and reported that only one (4%) had a second episode of neutropenia, suggesting that lithium improved the probability of success. A systematic review[15] including the two studies mentioned above reported 112 cases of rechallenge following neutropenia of which 34 (30%) failed, and 15 rechallenges following agranulocytosis of which 12 (80%) experienced further dyscrasia.

Further evidence guiding the selection of patients for rechallenge based on their previous haematological profile is therefore needed, as is evidence regarding the utility of treatments aimed at augmenting leucocyte counts. Observational studies of clozapine rechallenge offer important insights in this regard.

The National Psychosis Unit (NPU) is a tertiary centre admitting patients from across the UK for the management of treatment-refractory schizophrenia. A significant proportion have previously discontinued clozapine due to haematological adverse events, and therefore form a unique population in which to study clozapine rechallenge. We report the outcomes of 19 adult inpatients selected for clozapine rechallenge following previous leucopenia or neutropenia, and examine whether particular clinical characteristics are associated with outcome. We focus on the efficacy, safety and tolerability of adjunctive measures including lithium and G-CSF.

Methods

All admissions to the NPU between 1 January 2007 and 31 December 2013 were screened for inclusion. Inclusion criteria comprised at least one previous episode of clozapine therapy discontinued due to concurrent leucopenia and/or neutropenia, and subsequent clozapine rechallenge on the unit. Leucopenia was defined as a white cell count (WCC) $<3.0 \times 10^9$/L, neutropenia as an absolute neutrophil count (ANC) $<1.5 \times 10^9$/L, and agranulocytosis as a ANC $<0.5 \times 10^9$/L.

Demographic information, psychiatric diagnosis, characteristics of each clozapine trial (duration, dose, neutrophil nadir, duration of neutropenia), alternative explanations for neutropenia (co-morbid medical conditions, benign ethnic neutropenia, co-prescription of drugs reported to have a definite or probable causal association with neutropenia and agranulocytosis[6; 16]), and the use of adjunctive treatments (lithium and G-CSF), were extracted from the patient record. Ethnic group was classified according to guidelines from the Office for National Statistics, UK[17]: White, Mixed, Asian (from any part of the Asian continent, including Chinese), Black, and Other ethnic group (including Arab).

Full blood counts during treatment and, where possible, complete historical blood counts were obtained. Successful rechallenge was defined as continued clozapine therapy until discharge from the unit, and unsuccessful rechallenge being defined as recurrence of leucopenia, neutropenia or agranulocytosis prior to discharge. Blood tests during the follow up period were performed in accordance with guidelines from the clozapine monitoring service[18] (weekly for the first 18 weeks, and at four-week intervals thereafter), with the exception of those with a BEN-pattern receiving G-CSF, who had an increased frequency of monitoring (twice-weekly or on alternate days) during the initial phase of treatment, on the advice of the haematologist.

The t-test for independent and matched samples was used to compare differences in age and between and within group differences in ANC, and the Mann-Whitney and Wilcoxon signed rank test to compare treatment duration between and within groups respectively. Categorical variables were compared using the chi-square test. All reported p-values are two-sided. Statistical analysis was undertaken using SPSS 22[19].

Approval was obtained from the Drugs and Therapeutics Committee, South London and Maudsley NHS Foundation Trust, and the study complies with the standards laid down in the Declaration of Helsinki.

Results

146 patients were admitted over the study period, of whom 51 were rechallenged with clozapine. Nineteen of these patients had experienced previous clozapine-associated neutropenia that resulted in treatment discontinuation; all had primary ICD-10 diagnoses of schizophrenia. Rechallenge was successful in 15 patients (79%), and unsuccessful in four (21%) (**table 1**). Fourteen had undergone one previous trial of clozapine and five had undergone two previous trials, four of which were successfully rechallenged. None of the patients selected for rechallenge had previous agranulocytosis, on the basis of evidence suggesting rechallenge in this group is highly unlikely to succeed[20].

	All patients N = 19	Successful rechallenge N = 15	Failed rechallenge N = 4
Patient characteristics			
Sex, n (%)			
Male	15 (79)	12 (80)	3 (75)
Female	4 (21)	3 (20)	1 (25)
Age at time of rechallenge: mean (SD)	30.7 (7.4)	29.0 (5.7)	37.0 (10.4)
Ethnicity, n (%)			
White	12 (63)	9 (60)	3 (75)
Black	3 (16)	3 (20)	0
Asian	2 (11)	2 (13)	0
Mixed	1 (5)	1 (7)	0
Other	1 (5)	0	1 (25)
First exposure characteristics			
ANC nadir on first exposure/ x 10^9/L, mean (range)	1.26 (0.70 – 1.90)	1.33 (0.80 – 1.90)	1.08 (0.70 – 1.50)
Treatment duration/ weeks: median (range)	28.6 (0.9 – 434.7)	28.6 (0.9 – 434.7)	34.6 (9.6 – 100.1)
Duration of break from clozapine treatment*/ weeks, median (range)	99.6 (4.0 – 660.0)	94.0 (4.0 – 544.7)	146.1 (56.9 – 660.0)
Rechallenge characteristics			
ANC nadir on rechallenge/ x 10^9/L, mean (range)	n/a	n/a	0.56 (0.16 – 0.86)
Duration of follow up**/ time to neutropenia/ weeks, median (range)	34 (3.0 – 88.4)	40.6 (8.0 – 88.4)	3.9 (3.0 – 5.7)
Duration of follow up to at least: n (%)			
3 months:		14 (93)	n/a
6 months:		13 (87)	
9 months:		8 (53)	
12 months:		5 (33)	
Treated with valproate on rechallenge n (%)		3 (20)	3 (75)

Table 1: Patient characteristics, times to neutropenia and neutrophil count nadir on first and rechallenge exposures to clozapine.
*In patients with more than one previous trial, the duration between the end of the first and beginning of the most recent trials are reported.
** Follow up is defined as time from re-initiation of clozapine until discharge from the ward, or to recurrence of neutropenia.

Unsuccessful rechallenge

All four unsuccessful rechallenges had pre-treatment ANC consistently above 2 x 10^9/L, thus not meeting criteria for benign neutropenia, and all developed neutropenia below 1.0 x10^9/L on rechallenge, and one developed agranulocytosis (**table 2**). Clozapine dose range at neutropenia onset was 175 – 350 mg/day. Mean age was significantly higher than those successfully rechallenged (t=2.10, p=0.05). Comparing unsuccessful and successful rechallenges, the difference in ANC nadir on first exposure was non-significant (t=1.4, p=0.18), and duration of initial exposure to clozapine was shorter, though this difference was not statistically significant (U=25.0, p=0.67). Onset of neutropenia on rechallenge was sooner (34.6 vs. 3.9 weeks, W=10.0, p=0.03) and more severe than following initial exposure (neutrophil nadir of 0.56 x10^9/L vs. 1.08 x10^9/L) though this was non- significant (t=1.7, p=0.19). The median time to recovery of neutrophils following rechallenge was 8 days (range 4 – 19). Three of four (75%) patients failing rechallenge were prescribed valproate on rechallenge, compared with 3/15 (20%) who were successfully rechallenged (chi-square= 4.42; p=0.07). All other co-prescribed drugs associated with neutropenia are outlined in **table 2**.

Patient	Age	Ethnic group	Duration of first exposure/ weeks	Duration of rechallenge /weeks	ANC nadir on first exposure cells x 10^9/L	ANC nadir on rechallenge cells x 10^9/L	Duration neutro-penia on rechallenge/ days	Concurrent medication on rechallenge
1	37	White	43	3	0.7	0.85	4	Lithium Valproate [b]
2[a]	51	White	100 10	3	1.5 0.9	0.16	9	Lithium Valproate [b] Amisulpride Sprinolactone [b] Ramipril [b]
3	26	White	9	4	0.8	0.36	7	Lithium G-CSF
4	34	Other	26	5	1.3	0.86	19	Lithium Valproate [b] G-CSF

Table 2: Characteristics of the four patients failing rechallenge.

[a] This patient had two previous trials, both discontinued due to neutropenia.

[b] Known association with neutropenia

Patient 1 had spontaneous recovery of ANC on discontinuation of clozapine. Patient 2 developed agranulocytosis and required hospital admission for treatment of febrile neutropenia, and ANC recovered. Patient 3 received G-CSF on developing neutropenia and continued to receive clozapine, in line with a plan agreed with haematologists. Despite this, agranulocytosis developed, at which point clozapine was discontinued and the patient transferred to a general hospital. Further G-CSF was administered and the patient made a good recovery. Patients 1-3 demonstrated a characteristic profile of a spike in ANC within a fortnight prior to neutropenia onset, and a rebound leucocytosis following resolution (**figure 1a)**.

Patient 4 experienced protracted neutropenia and leucopenia on week five of treatment, after which clozapine was discontinued and G-CSF administered 19 days after the onset of neutropenia. A robust granulopoeitic response was observed (peak ANC of 15.2 and WCC of 17.7). Due to continued severe psychotic symptoms, a further rechallenge with clozapine was reattempted four months later following haematological consultation, with concurrent G-CSF cover (not shown in table 2). The response to G-CSF was however attenuated (ANC range 2.03 – 5.38; WCC 2.86 – 6.74) and ANC continued a downward trend. Rechallenge was abandoned after 25 days, and ANC normalised following discontinuation of clozapine.

Successful rechallenge

Following haematological consultation, 5/15 (33%) of the successfully rechallenged patients were diagnosed with BEN on the basis of a pre-clozapine ANC persistently below normative thresholds, their ethnicity (Black (n= 3), Asian (n=1) and Mixed (n=1)) and an absence of alternative explanations for persistent neutropenia. For these patients, the use of modified monitoring criteria[10] was agreed with the clozapine monitoring service prior to clozapine initiation, with an initially increased frequency of blood monitoring (twice a week for the first 12 weeks). In all cases, other agents known to cause neutropenia were discontinued prior to initiation, and lithium augmentation was trialled at a therapeutic dosage (>0.4 mmol/L 12 hours post-dose) and continued in all but one patient.

Despite the use of lithium and BEN monitoring criteria, the baseline pre-clozapine ANC in two patients frequently fell below 1.0 x 10^9/L, and was too low to permit initiation and maintenance of clozapine. G-CSF was therefore administered on a twice-weekly basis prior to and throughout clozapine treatment to allow continued dispensing of clozapine by the monitoring service (**figure 1b)**. Granocyte® 105 mcg twice weekly (lenograstim, Chugai, Tokyo, Japan) and Neupogen® 150 mcg twice weekly (filgrastim, Amgen, Vienna, Austria) were administered subcutaneously in either case; further details of the G-CSF administration protocol are described in a previously published case report [12]. No significant side-effects of G-CSF were reported.

Though their ethnicity precluded a formal diagnosis of BEN, 8/15 (53%) of the successfully rechallenged patients demonstrated a similar pattern of constitutionally low neutrophils that preceded clozapine treatment, with fluctuating pre-clozapine neutrophil counts whose lower limit frequently neared, or breached, the lower threshold of 2.0 x 10^9/L. Seven were White, and one was Asian. Alternative reasons for neutropenia were excluded, and where possible other drugs associated with neutropenia were discontinued. Six patients received lithium for ANC augmentation, and four had a plan agreed with a haematologist for G-CSF administration in the event of a neutropenia in the low-amber (near 1.5 x 10^9/L) or red (<1.5 x 10^9/L) range. Two patients received a single dose of G-CSF following an amber or red neutropenia, and were able to continue treatment (**figure 1c**).

The remaining 2/15 (13%) successfully rechallenged patients were White, and did not have an ANC at baseline consistent with chronic neutropenia. Both were prescribed lithium. One patient had a sustained drop in baseline ANC four weeks after clozapine initiation, as shown in **figure 1d**.

Additional co-prescribed medications in the 10 patients without BEN were lamotrigine (n = 2), valproate (n = 3), amisulpride (n = 2) and aripiprazole (n = 1). Of these, lamotrigine and valproate are associated with neutropenia.

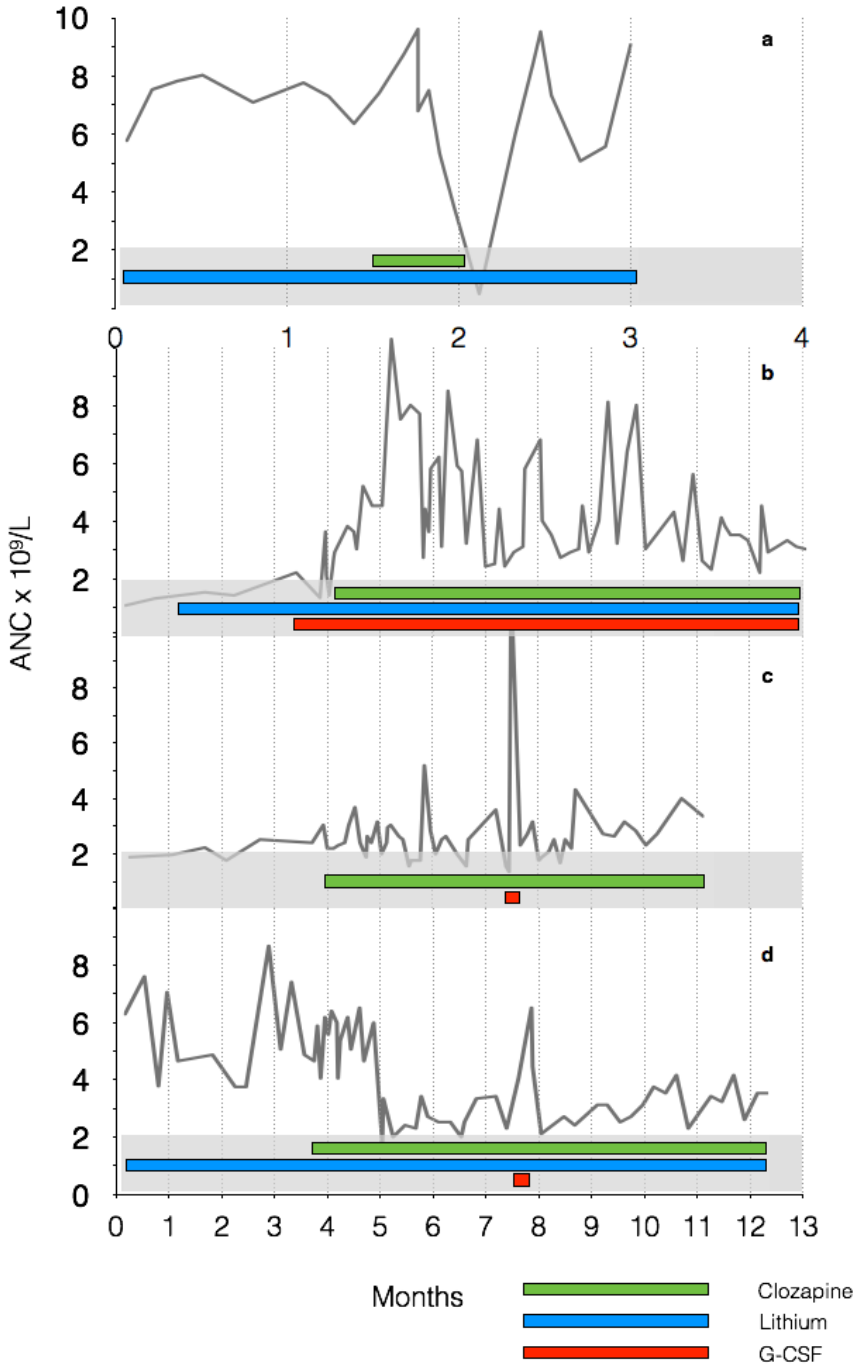

Figure 1: illustrative haematological profiles of failed (a) and successful (b – d) rechallenges. 0 on the ordinal axis indicates admission; note different scale in figure (a). **1a:** agranulocytosis with spontaneous recovery in patient 2, note spike in ANC prior to neutropenia, and rebound on recovery. **1b:** BEN patient, administered G-CSF on a twice weekly basis. **1c**: White patient with low baseline ANC. Spike represents administration of G-CSF following red result. **1d**: White patient who developed a drop in mean ANC four weeks after commencing clozapine but was able to continue treatment with lithium and a single administration of G-CSF.

Discussion

In this the third largest series of clozapine rechallenge in adults, we have shown that in a selected group of inpatients with severe treatment refractory illness, 15/19 (79%) of patients were successfully re-established on clozapine following previous treatment-emergent leucopenia or neutropenia. This is higher than that of Dunk and colleagues[13] reporting successful rechallenge in 62% (32/52), and comparable to the 24/25 (96%) success rate reported previously by our unit[14]. We believe this demonstrates the importance of carefully selecting patients who have a relatively reduced risk of a neutropenia based on their previous history, and optimising rechallenge with adjunctive treatments.

The mechanisms of clozapine-induced neutropenia and agranulocytosis remain uncertain[21]. There may exist a unitary process, where neutropenia progresses inevitably to agranulocytosis if clozapine is not terminated[21]. An alternative hypothesis posits two distinct mechanisms, one leading to agranulocytosis, and another to persistent neutropenia but not agranulocytosis[6].

Given that the haematological outcomes on rechallenge are likely to reflect the cause underlying discontinuation in earlier trials, we hypothesise the following categories based on the rechallenge outcomes observed in our cohort: 1) clozapine-induced agranulocytosis, or neutropenia that would otherwise have progressed to agranulocytosis, with a characteristic pattern and time-course; 2) persistent neutropenia that does not progress to agranulocytosis that may be related to clozapine but also the co-prescription of other agents, and 3) idiopathic, persistent neutropenia (not restricted to those with ethnicity associated with BEN) unrelated to clozapine or other agents. We suggest that groups 2 and 3 can be considered for rechallenge with specialist input.

Factors associated with unsuccessful rechallenge

Consistent with established findings that age is a risk factor for clozapine-induced dyscrasia[3; 4], patients who developed neutropenia on rechallenge were significantly older. Similar to the finding by Dunk et al[13], patients who failed rechallenge had a more severe and rapid onset of subsequent neutropenia, suggesting an immune-mediated mechanism.

Three out of four patients developing neutropenia on rechallenge showed a spike in ANC in the fortnight preceding dyscrasia, a phenomenon which was found to be a sensitive but non-specific predictor of agranulocytosis[22]. A possible mechanism is the production of endogenous granulopoeitic factors that initially compensates for the incipient fall in granulocytes. The response to G-CSF was attenuated in two patients who failed rechallenge, in comparison to BEN patients whose granulopoietic response did not diminish despite successive administrations or G-CSF. This suggests that attenuation in response to G-CSF is an indicator of injury to the granulocyte precursors in the bone marrow, and that clozapine should be discontinued immediately.

Factors associated with successful rechallenge

Successful rechallenge was associated with a shorter median duration of first exposure to clozapine: one explanation might be that these patients failed their first trial early in treatment due to constitutionally low neutrophils, and not clozapine toxicity. Over half of the successfully rechallenged patients were White, and therefore ineligible for BEN criteria, but nonetheless had consistently low pre-clozapine ANC. This is consistent with previous studies[9] that suggest ANCs at the lower end of the population distribution in otherwise asymptomatic individuals is a common reason for clozapine discontinuation, and does not necessarily indicate clozapine toxicity. Therefore, correctly identifying this haematological pattern is critical in selecting patients who are likely to be successfully rechallenged. Four out of five patients who had undergone more than one previous trial were successfully rechallenged, suggesting that multiple trials are not necessarily associated with unsuccessful rechallenge.

Treatment with lithium and G-CSF

All of the patients who developed neutropenia on rechallenge were prescribed lithium, suggesting that, in these patients, it does not protect against clozapine-induced neutropenia. Similarly, responses to G-CSF were attenuated in patients who failed rechallenge, also arguing that G-CSF is not protective against clozapine-induced neutropenia in these patients.

Of the successful rechallenges, 4/5 of the BEN patients and 8/10 of the remaining patients received lithium, suggesting that lithium has utility in increasing ANC and avoiding treatment discontinuation. Two BEN patients received regular G-CSF, and three White patients received single doses of G-CSF, indicating that G-CSF can also play a role in facilitating uninterrupted treatment with clozapine.

However, lithium may compromise neutrophil function[23; 24], and no studies have investigated the rate of infection in lithium treatment. Furthermore, the use of G-CSF in allowing continued clozapine therapy is contentious. In addition to commonly reported acute side-effects such as bone pain[25] in patients receiving G-CSF following chemotherapy, the safety of long-term treatment with G-CSF is unknown. Osteopenia[26] and splenic enlargement[27] have been described, and we recommend monitoring of bone density and spleen size in long-term G-CSF use.

Implications for clinical practice and future research

Our findings suggest that current concepts of BEN are too narrow, and leads to unnecessary discontinuation of clozapine in those with a picture of idiopathic neutropenia. ANCs of 0.5 – 1.5 x 10^9/L, defined haematologically as 'mild to moderate neutropenia' are not associated with a significantly increased risk of infection[28]. Consideration should therefore be given the use of lowered thresholds to patients of other ethnicities, following haematological evaluation. The use of definitions such as chronic idiopathic neutropenia [29] may aid this process. Future approaches to differentiating clozapine-induced neutropenia from incidental neutropenia unrelated to clozapine may include consideration of dynamic trends in ANC relative to an individual's baseline pre-clozapine ANC, rather than the absolute counts relative to an arbitrary threshold.

We could not clearly identify a subset of patients who develop a milder form of clozapine-induced neutropenia, although the trend in one case (**figure 1d**) did support the existence of such a pattern. Further work is necessary to identify whether clozapine can cause a milder neutropenia, or induces fluctuations in ANC.

Where possible, other drugs associated with neutropenia were stopped prior to rechallenge. However, 3/4 (75%) patients failing rechallenge were co-prescribed valproate, compared to 3/15 (20%) who were successfully rechallenged. Clozapine in combination with valproate has been associated with a greater risk of neutropenia

than with either drug alone[30], and a case of treatment-emergent neutropenia with clozapine and valproate that resolved on withdrawal of valproate has been reported[31]. When considering rechallenge, the potential role of valproate in contributing to neutropenia should be borne in mind.

The requirement for haematological monitoring has led to a greater awareness of clozapine-induced neutropenia. However, other serious medical complications such as cardiomyopathy, ileus or diabetic ketoacidosis are reported to have caused more deaths than agranulocytosis[32], and deserve equal emphasis. Future research should examine the relative risks of all complications, not only haematological, as well as the circumstances in which rechallenge may be appropriate. Finally, the benefits of clozapine in reducing suicide[33] and overall mortality[34; 35] must be balanced against these risks.

Limitations

Clozapine rechallenge is a rare occurrence, and the small number of cases reported here reflects this. The statistical analyses and conclusions in relation to the unsuccessful rechallenge group should therefore be interpreted with caution. A further limitation of this study arises from its retrospective observational design. Follow-up ended when patients were discharged from the service, with a median duration of follow-up in successfully rechallenged patients of 41 weeks. It is therefore possible that some of these individuals developed neutropenia after discharge. However, other rechallenge studies with longer follow-up found a median time to dyscrasia of 5.5 weeks[13], suggesting that most dyscrasia occurs soon after restarting clozapine.

The severity of psychosis in our patient group did not permit a drug-free period prior to clozapine initiation. Therefore, other antipsychotics associated with neutropenia such as olanzapine and risperidone[6] may have contributed to the persistent pre-clozapine neutropenia observed in some patients. It remains extremely difficult to demonstrate that a given drug contributes to dyscrasia when prescribed in conjunction with clozapine, and case reports have been conflicting[36].

The highly selected patient group and setting may limit the generalizability of our findings; patients with BEN or other benign neutropenia may be over-represented in our sample, and not all centres will have experience in using G-CSF. Definitions of

ethnic groups are imprecise[37], and the categories used in this study overlook the significant diversity that exist within populations.

Clinical points

- Neutropenia is a frequent reason for discontinuing clozapine, and there is often uncertainty over attempting rechallenge.

- This study suggests that with careful selection and support from a haematologist, some patients can be successfully rechallenged following neutropenia.

- Look carefully at circumstances of initial neutropenia. Consider whether benign ethnic neutropenia (BEN), co-prescribed medications and medical conditions could have been responsible.

- In cases of BEN, lithium and G-CSF may aid rechallenge. White patients can also present with a picture of persistent neutropenia identical to BEN.

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